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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/736,902	12/17/2003	David Brown	P24170	4047

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EXAMINER	
SHEIKH, HUMERA N	
ART UNIT	**PAPER NUMBER**
1615	

NOTIFICATION DATE	DELIVERY MODE
11/23/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gbpatent@gbpatent.com
pto@gbpatent.com

Office Action Summary	Application No.	Applicant(s)	
	10/736,902	BROWN ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) *25, 26 and 39-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24,27-38 and 68-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Response after Non-Final Office Action and Applicant's Arguments/Remarks, all filed 08/31/07 is acknowledged.

Claims 1-74 are pending in this action. No amendments to the claims have been made. Claims 25, 26 and 39-67 have previously been withdrawn (due to non-elected invention). Claims 1-24, 27-38 and 68-74 remain rejected.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

(1) Claims 1-24, 27-38 and 68-74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-98 of copending Application No. 10/798,884 ('884 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because similar subject matter has been claimed in each of the copending applications.

The first drug of the instant application is promethazine, whereas the first drug of the copending '884 application is morphine and pharmaceutically acceptable salts thereof. However, it would be obvious to one of ordinary skill in the art to incorporate any suitable active agents that are biocompatible, each with the other. While the '884 copending application claims a first drug being morphine derivatives having antitussive activity, it is noted that the instant application demonstrates that additional active agents, such as antitussives, can also be used in the composition (see instant claims 4 &5). Thus, there would be ample motivation to use the morphine derivatives having antitussive activity of '884 within the pharmaceutical dosage of the instant application, since the instant application recognizes that antitussives are also useful in their composition.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

* * * * *

(2) Claims 1-24, 27-38 and 68-74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-101 of copending

Application No. 10/910,806 ('806 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because similar subject matter has been claimed in each of the copending applications.

The first drug of the instant application is promethazine, whereas the first drug of the copending '806 application is carbetapentane and pharmaceutically acceptable salts thereof. However, it would be obvious to one of ordinary skill in the art to incorporate any suitable active agents that are biocompatible, each with the other. While the '806 copending application claims a first drug being carbetapentane, which is a cough suppressant/expectorant, it is noted that the instant application demonstrates that additional active agents, such as expectorants can also be used in the composition (see instant claims 10-11). Thus, there would be ample motivation to use the cough suppressant/expectorant, carbetapentane of '806 within the pharmaceutical dosage of the instant application, since the instant application recognizes that cough suppressants/expectorants are also useful in their composition.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

* * * * *

(3) Claims 1-24, 27-38 and 68-74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-128 of copending Application No. 10/939,351 ('351 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because similar subject matter has been claimed in each of the copending applications.

The first drug of the instant application is promethazine, whereas the first drug of the copending '351 application is phenylepherine and pharmaceutically acceptable salts thereof. However, it would be obvious to one of ordinary skill in the art to incorporate any suitable active agents that are biocompatible, each with the other. While the '351 copending application claims a first drug being phenylepherine, which is a decongestant, it is noted that the instant application demonstrates that additional active agents, such as decongestants (i.e., phenylepherine) can also be used in the composition (see instant claims 6-7). Thus, there would be ample motivation to use the decongestant, phenylepherine of '351 within the pharmaceutical dosage of the instant application, since the instant application recognizes that decongestants (i.e., phenylephereine) are also useful in their composition.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

* * * * *

(4) Claims 1-24, 27-38 and 68-74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-84 of copending Application No. 11/012,267 ('267 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because similar subject matter has been claimed in each of the copending applications.

The first drug of the instant application is promethazine, whereas the first drug of the copending '267 application is diphenhydramine and pharmaceutically acceptable salts thereof. However, it would be obvious to one of ordinary skill in the art to incorporate any suitable active agents that are biocompatible, each with the other. While the '267 copending application claims

a first drug being diphenhydramine, which is a antihistamine, it is noted that the instant application demonstrates that additional active agents, such as antihistamines can also be used in the composition (see instant claims 8-9). Thus, there would be ample motivation to use the antihistamine, diphenhydramine of '267 within the pharmaceutical dosage of the instant application, since the instant application recognizes that antihistamines are also useful in their composition.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

* * * * *

(5) Claims 1-24, 27-38 and 68-74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-156 of copending Application No. 11/115,321 ('321 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because similar subject matter has been claimed in each of the copending applications.

The first drug of the instant application is promethazine, whereas the first drug of the copending '321 application is selected from decongestants, antitussives, expectorants, analgesics and antihistamines. However, it would be obvious to one of ordinary skill in the art to incorporate any suitable active agents that are biocompatible, each with the other. It is noted that the instant application demonstrates that additional active agents, such as antihistamines, antitussives, expectorants and decongestants can also be used in the composition (see instant claim 2). It is also noted that the '321 copending application also claims the use of suitable antihistamines, such as promethazine (see claims 12-13 of '321). Thus, there would be ample

motivation to use the antihistamine, promethazine of '321 within the pharmaceutical dosage of the instant application, and there would be ample motivation to use the antitussives, expectorants and decongestants of '321 within the instant application, since the instant application recognizes that suitable drugs (antihistamines, antitussives, expectorants, decongestants) are also useful in their composition.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

* * * * *

(6) Claims 1-24, 27-38 and 68-74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-44 of copending Application No. 11/102,725 ('725 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because similar subject matter has been claimed in each of the copending applications.

The first drug of the instant application is promethazine and the first drug of the copending '725 application is also promethazine and pharmaceutically acceptable salts thereof. The claims differ in the duration of the plasma concentration range ('725 recites plasma concentration for at least about 24 hours). However, suitable plasma concentration range and duration of therapeutic effects can be determined by one of ordinary skill in the art through routine experimentation. It is also noted that '725 claims a second further drug (see claims 16-17), as does the instant application. It would be obvious to one of ordinary skill in the art to incorporate any suitable active agents that are biocompatible, each with the other. There would

be ample motivation to use the additional drugs disclosed in the '725 application within the instant application, since the instant application recognizes the use of the same drugs and recognizes the drugs to be useful in their composition.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

* * * * *

(7) Claims 1-24, 27-38 and 68-74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-44 of copending Application No. 11/102,726 ('726 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because similar subject matter has been claimed in each of the copending applications.

The first drug of the instant application is promethazine, whereas the first drug of the copending '726 application is diphenhydramine and pharmaceutically acceptable salts thereof. However, it would be obvious to one of ordinary skill in the art to incorporate any suitable active agents that are biocompatible, each with the other. While the '726 copending application claims a first drug being diphenhydramine, which is a antihistamine, it is noted that the instant application demonstrates that additional active agents, such as antihistamines can also be used in the composition (see instant claims 8-9). Thus, there would be ample motivation to use the antihistamine, diphenhydramine of '726 within the pharmaceutical dosage of the instant application, since the instant application recognizes that antihistamines are also useful in their composition.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

* * * * *

(8) Claims 1-24, 27-38 and 68-74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-55 of copending Application No. 11/115,293 ('293 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because similar subject matter has been claimed in each of the copending applications.

The first drug of the instant application is promethazine, whereas the first drug of the copending '293 application is selected from decongestants, antitussives, expectorants, mucus thinning drugs, analgesics and antihistamines. However, it would be obvious to one of ordinary skill in the art to incorporate any suitable active agents that are biocompatible, each with the other. It is noted that the instant application demonstrates that additional active agents, such as antihistamines, antitussives, expectorants and decongestants can also be used in the composition (see instant claim 2). It is also noted that the '293 copending application also claims the use of suitable antihistamines, such as promethazine (see claim 2 of '293). Thus, there would be ample motivation to use the antihistamine, promethazine of '293 within the pharmaceutical dosage of the instant application, and there would be ample motivation to use the antitussives, expectorants and decongestants of '293 within the instant application, since the instant application recognizes that suitable drugs (antihistamines, antitussives, expectorants, decongestants) are also useful in their composition.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

* * * * *

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-24, 27-38 and 68-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanara *et al.* (U.S. Pat. No. 6,699,502) in view of Findlay *et al.* (U.S. Pat. No. 4,650,807).

The instant invention is drawn to a pharmaceutical dosage form which comprises (a) a first drug which is at least one of promethazine and a pharmaceutically acceptable salt thereof and (b) at least one second drug, wherein the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

Fanara *et al.* ('502) teach oral pharmaceutical compositions for controlled release of active substances, whereby the compositions include multi-layered formulations. The compositions can be administered in a few daily doses, ideally in a single daily dose (see column

1, lines 5-13 and Abstract). The release of active substances during oral administration can be controlled by means of matrix-type pharmaceutical compositions (col. 1, lines 14-16).

According to Fanara, it is increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after administration. In the case where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles (col. 2, lines 36-50).

The compositions allow regular and continuous release of active substances over periods of at least 12 hours (col. 3, lines 28-31).

The controlled release compositions can be used in combination with an immediate release pharmaceutical composition for the same or for another active substance, in a single unit intended to be administered orally (col. 2, lines 32-37).

Suitable active substances disclosed include antihistamines, analgesics, antitussives and the like (col. 4, lines 57-58). Specific active substances taught include decongestants, such as pseudoephedrine, phenylepherine, phenylpropanolamine and antitussives such as hydrocodone, codeine, morphine, their optimal isomers or pharmaceutically acceptable salts (col. 4, lines 58-67).

The pharmaceutical compositions are provided in the form of tablets, of which bi-layered and multi-layered tablets are also included (col. 5, line 15 – col. 6, line 25).

The Examples at columns 6-18 demonstrate various layered controlled release pharmaceutical compositions of the invention. For instance, Example 7 at column 12, demonstrates a double-layered tablet comprising hydrocodone bitartrate. The double layered-tablets contained 15 mg doses of hydrocodone consisting of a controlled-release layer containing a 10 mg dose of hydrocodone and an immediate-release layer containing a 15 mg dose of hydrocodone. The results showed that 35% of hydrocodone was already released after 1 hour, which corresponds to the hydrocodone content in the immediate release layer (33.3% of the total dose). The release of the hydrocodone continued gradually and regularly (col. 12, line 24 – col. 13, line 26).

With respect to the instant claim limitation of the "dosage form providing a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70% of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug", it is the position of the Examiner that the Fanara reference meets these claim limitations. The Fanara reference explicitly recognizes and teaches simultaneous administration of multiple active agents whereby it is possible to combine therapeutic effects of active substances having very different pharmacokinetic profiles. Thus, the Fanara reference teaches an objective similar to that being claimed by Applicant.

With regards to the plasma half-lives claimed, it is noted that the Fanara reference teaches similar active ingredients as claimed and thus, the plasma half-lives would be expected to be the same as that claimed herein by Applicant.

Regarding the limitation of the 'tablet comprising a matrix with the first drug and particles which comprise the second drug', the Examiner points out that Fanara teaches the use

of layered, both bi-layered and multi-layered tablets and thus, this limitation is also met by the primary reference.

Fanara *et al.* teach antihistamines (col. 4, line 58). Fanara et al. do not teach the antihistamines promethazine and chlorpheniramine and do not teach the antitussive-expectorant, guaifenesin.

Findlay *et al.* ('807) teach antihistaminic compositions, which can be in the form of tablets (col. 1, lines 6-25); (col. 5, lines 33-50). Suitable antihistamines taught include *pheniramines and promethazine* (col. 1, lines 26-31). Findlay *et al.* teach that the active compound may be formulated with a sympathomimetic agent such as decongestants (pseudoephedrine, phenylpropanolamine), an antitussive (i.e., codeine), an analgesic, anti-inflammatory or an antitussive-expectorant such as *guaifenesin* (col. 5, lines 1-21). The compositions are free from sedative effects and have little or no anticholinergic effects (Abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the suitable antihistamines and expectorants taught by Findlay *et al.* within the formulations of Fanara *et al.* One of ordinary skill in the art would be motivated to do so with a reasonable expectation of success because Findlay et al. teach antihistamines, such as pheniramines and promethazine and antitussive-expectorants, such as guaifenesin, which are useful for their histamine-blocking and cough suppressing properties. The expected result would be an improved formulation for the treatment of cough suppression and allergic conditions.

With regards to particular amounts of active agents, the Examiner points out that generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

* * * * *

Claims 1-24, 27-38 and 68-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanara *et al.* (U.S. Pat. No. 6,699,502) in view of Paradissis *et al.* (U.S. Pat. No. 5,445,829).

The instant invention is drawn to a pharmaceutical dosage form which comprises (a) a first drug which is at least one of promethazine and a pharmaceutically acceptable salt thereof and (b) at least one second drug, wherein the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

Fanara *et al.* ('502) teach oral pharmaceutical compositions for controlled release of active substances, whereby the compositions include multi-layered formulations. The compositions can be administered in a few daily doses, ideally in a single daily dose (see column

1, lines 5-13 and Abstract). The release of active substances during oral administration can be controlled by means of matrix-type pharmaceutical compositions (col. 1, lines 14-16).

According to Fanara, it is increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after administration. In the case where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles (col. 2, lines 36-50).

The compositions allow regular and continuous release of active substances over periods of at least 12 hours (col. 3, lines 28-31).

The controlled release compositions can be used in combination with an immediate release pharmaceutical composition for the same or for another active substance, in a single unit intended to be administered orally (col. 2, lines 32-37).

Suitable active substances disclosed include antihistamines, analgesics, antitussives and the like (col. 4, lines 57-58). Specific active substances taught include decongestants, such as pseudoephedrine, phenylepherine, phenylpropanolamine and antitussives such as hydrocodone, codeine, morphine, their optimal isomers or pharmaceutically acceptable salts (col. 4, lines 58-67).

The pharmaceutical compositions are provided in the form of tablets, of which bi-layered and multi-layered tablets are also included (col. 5, line 15 – col. 6, line 25).

The Examples at columns 6-18 demonstrate various layered controlled release pharmaceutical compositions of the invention. For instance, Example 7 at column 12, demonstrates a double-layered tablet comprising hydrocodone bitartrate. The double layered-tablets contained 15 mg doses of hydrocodone consisting of a controlled-release layer containing a 10 mg dose of hydrocodone and an immediate-release layer containing a 15 mg dose of hydrocodone. The results showed that 35% of hydrocodone was already released after 1 hour, which corresponds to the hydrocodone content in the immediate release layer (33.3% of the total dose). The release of the hydrocodone continued gradually and regularly (col. 12, line 24 – col. 13, line 26).

With respect to the instant claim limitation of the "dosage form providing a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70% of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug", it is the position of the Examiner that the Fanara reference meets these claim limitations. The Fanara reference explicitly recognizes and teaches simultaneous administration of multiple active agents whereby it is possible to combine therapeutic effects of active substances having very different pharmacokinetic profiles. Thus, the Fanara reference teaches an objective similar to that being claimed by Applicant.

With regards to the plasma half-lives claimed, it is noted that the Fanara reference teaches similar active ingredients as claimed and thus, the plasma half-lives would be expected to be the same as that claimed herein by Applicant.

Regarding the limitation of the 'tablet comprising a matrix with the first drug and particles which comprise the second drug', the Examiner points out that Fanara teaches the use

of layered, both bi-layered and multi-layered tablets and thus, this limitation is also met by the primary reference.

Fanara *et al.* teach antihistamines (col. 4, line 58). Fanara et al. do not teach the antihistamines promethazine and chlorpheniramine and do not teach the expectorant, guaifenesin.

Paradissis *et al.* ('829) teach extended release pharmaceutical compositions containing both an immediate release formulation and an extended release formulation, whereby the compositions are preferably in the form of a tablet (see col. 1, lines 15-26). The compositions include pharmaceutically active compounds, such as antihistamines, antitussives, expectorants and decongestants (col. 3, lines 34-41). Suitable antihistamines taught include chlorpheniramine maleate and promethazine. Suitable antitussive-expectorants taught include guaifenesin (col. 4, lines 39-47).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the suitable antihistamines and antitussive-expectorants taught by Paradissis *et al.* within the formulations of Fanara *et al.* One of ordinary skill in the art would be motivated to do so with a reasonable expectation of success because Paradissis *et al.* teach pharmaceutical compositions comprising effective antihistamines, such as chlorpheniramine and promethazine and teach antitussive-expectorants, such as guaifenesin, which are known to be useful for their histamine-blocking and cough suppressing effects. The expected result would be an enhanced formulation for treating cough and allergic conditions.

With regards to particular amounts of active agents, the Examiner points out that generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Pertinent Art:

Prior art made of record and cited of interest:

- **Shimizu *et al.*** (U.S. Pat. No. 6,586,004)

  Shimizu et al. teach solid preparations comprising antihistamines, such as promethazine and chlorpheniramine maleate and antitussive-expectorants, such as guaifenesin (see col. 3, lines 13-31).

Response to Arguments

Applicant's arguments filed 08/31/07 have been fully considered but they are not persuasive.

Double Patenting Rejection:

Applicant argued, "All claims under consideration are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims of co-pending application Nos. 10/798,884, 10/910,806, 10/939,351, 11/012,267, 11/115,321, 11/102,725, 11/102,726 and 11/115,293. Applicants respectfully request that these rejections be held in abeyance until the Examiner has indicated allowable subject matter. Applicants will then decide if the filing of one or more Terminal Disclaimers is warranted."

Examiner acknowledges Applicant's request to hold the pending non-statutory obviousness-type double patenting rejections in abeyance until notification of allowable subject matter. The double patenting rejections have been maintained herein, since the claims at present are neither allowed or indicated as allowable and Terminal Disclaimers over the above-listed pending applications have not yet been filed.

Rejection under 35 U.S.C. 103(a) over Fanara (USPN 6,699,502) in view of Findlay (USPN 4,650,807):

Applicant argued, "Fanara is primarily concerned with pharmaceutical compositions for the controlled release of active substances, not with the simultaneous administration of active substances."

This argument has been fully considered, but was not deemed persuasive. Fanara explicitly teaches on col. 2, lines 36-50, as identified by Applicant that it is "therapeutically advantageous to be able to simultaneously administer by the oral route an active substance...". The reference clearly suggests that the active substance can be administered simultaneously as also desired by Applicant. Moreover, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., simultaneous administration of active substances) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus, Applicant's arguments do not establish the scope of claims being presented.

Applicant argued, "Fanara mentions exclusively immediate release/controlled release combinations, i.e., combinations which provide different release rates of the active substances, but is completely silent with respect to the duration of action of the active substances, let alone the duration of action of one drug in relation to the duration of action of the other drug."

This argument was not persuasive since Applicants are not claiming a specific drug release profile of the first and second active substances, which would patentably define and distinguish over the release rates suggested by Fanara. Applicant argues, "Fanara is silent with respect to the duration of action of the active substances". This was not found persuasive since the Examiner notes that the instant claims are also silent with regards to claiming duration of action of any of the active substances. Furthermore, as noted above, the active substances of Fanara can be administered simultaneously. Applicant's claims are generic in terms of any specific release rates. Thus, the teachings of Fanara are sufficient to meet the instant claim limitations.

Applicant argued, "Only with hindsight is it possible to conclude that the plasma concentrations of the two active substances should be in therapeutic range over similar or substantially coextensive periods of time."

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant argued, "The term 'pharmacokinetic profile' encompasses a wide range of properties of a drug. The Examiner has failed to provide any (written or other) evidence which shows that differences in release rates of different active substances from a single dosage form result in and/or are conventionally used to provide plasma concentrations in a therapeutic range

of two active substances which are present in the single dosage form over similar or substantially coextensive periods of time."

The Examiner was not persuaded by this argument since the limitation relating to the plasma concentration in independent claim 1 is generic in terms of any specific release rates desired and in terms of duration of the period intended. The limitation "over a period..." is vague and does not refer to any specific extent or duration over which the plasma concentration of the first and second active substance should overlap. Moreover, Applicants have not established any unexpected results which accrue based on the plasma concentration limitations. No patentability is seen in the generic limitations being claimed herein. The prior art vividly teaches the release of active substances, suitable for controlled release using matrix-type pharmaceutical compositions and further teaches the same class of compounds being claimed by Applicant. The claims remain generic enough to read on the teachings of Fanara.

Applicant argued, "As set forth in, e.g., paragraphs [0002] and [0044] of the present specification, a single dose of promethazine hydrochloride can provide a therapeutically effective plasma concentration for an extended period of time, up to 12 hours and even longer, whereas a single dose of an expectorant such as guaifenesin will usually provide relief for only about one hour and decongestants, antitussives and analgesics usually provide relief for about 4 to 8 hours per single dose."

This argument was not persuasive. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicants arguments do not demonstrate the scope of claims instantly presented herein.

Applicant argued, "Applicants fail to see why a (bi- or multi-)layered tablet allegedly is the same as a tablet comprising a matrix which comprises a drug and has dispersed therein particles which comprise a second drug".

Examiner notes that Fanara teaches the pharmaceutical compositions are provided in the form of tablets, of which bi-layered and multi-layered tablets are also included (col. 5, line 15 – col. 6, line 25) as well as matrix-type pharmaceutical compositions (col. 1, lines 14-16).

Applicant argued, "Findlay does not teach that suitable antihistamines for the composition include pheniramines and promethazine. Fanara would provide a disincentive rather than a motivation to include an antihistamine such as promethazine in one of the compositions disclosed by the former document."

This argument was not persuasive. Findlay amply remedies the deficiency of Fanara for the teaching of the particular antihistamine – promethazine and pheniramine and the antitussive/expectorant - guaifenesin. The reference recognizes that the use of such antihistamines is well known, albeit, with certain side effects. The reference teaching, nonetheless, would not deter one of ordinary skill in the art from using the particular antihistamines for their known beneficial effects, i.e., histamine antagonistic effects. The reference further teaches that guaifenesin is a suitable expectorant for use in their invention. Thus, Findlay is sufficient to overcome this deficiency of Fanara.

Rejection under 35 U.S.C. 103(a) over Fanara (USPN 6,699,502) in view of Paradissis (USPN 5,445,829):

Applicant argued, "Paradissis, like Fanara and Findlay, is unable to render obvious to one of ordinary skill in the art to provide a dosage form which comprises (any) two different active substances and provides similar or substantially coextensive periods of therapeutic activity of these two different active substances."

This argument was not persuasive. Applicants claims are generic in the sense that the claims do not require a specific drug release profile of the first and second active substances, which would patentably distinguish over the release rates suggested by the primary reference of Fanara. Applicant's claims simply desire some overlapping or coextension of therapeutic activity, whereby it is noted that the prior art could also achieve this effect. The prior art explicitly teaches simultaneous administration of active ingredients. Absent a showing of evidence to the contrary, the formulations of the prior art would be capable of providing overlap

of therapeutic activity between the first and second active substances. Moreover, Paradissis was relied upon for the teaching of antihistamines – chlorpheniramine and promethazine as well as the antitussive/expectorant – guaifenesin and thus is ample for all that it teaches.

Applicant argued, "Paradissis fails to provide any motivation for one of ordinary skill in the art to employ promethazine, which is mentioned in the laundry list of exemplary substances and which is not included in the list of preferred drugs, in combination with any of the other exemplary drugs."

This argument was not persuasive since Paradissis clearly teaches promethazine as one of the suitable and effective antihistamines that can be used in their formulation. Preferred as well as non-preferred embodiments of the reference are taken into consideration for determining grounds for obviousness.

Applicant argued, "It is noted that in two of the Examples of Paradissis, combinations of drugs are employed. However, in both of these examples, the active ingredients are blended together prior to being formulated into the particles and thus, they are both present in the immediate release particles as well as in the extended release particles. In view thereof, it is to be expected that both drugs have very similar release (dissolution) profiles."

This argument was not persuasive since the instant claim language does not exclude the active ingredients from being initially blended together, whereby both active ingredients would be provided in immediate and extended release form. Furthermore, the instant claims are drawn to a composition, and not a process of producing the dosage form. Thus, Applicant's arguments relating to the particular process by which the prior art combines the active ingredients prior to formulation into the particles was not found persuasive.

Lastly, Applicant argued, "Even if one were to assume, *arguendo,* that one of ordinary skill in the art would be motivated to replace the chlorpheniramine maleate of Examples 2 and 3 of PARADISSIS with promethazine and/or a pharmaceutically salt thereof, this would not render obvious any of the claimed subject matter because, as set forth above and in the present specification, promethazine can provide a therapeutically effective plasma concentration for an extended period of time, up to 12 hours and even longer, and it is apparent that a dosage form which comprises promethazine in an extended release formulation will even prolong this period rather then shorten it to better match it with the duration of the action of any other drugs combined therewith."

This argument has been considered, but was not persuasive. Applicant's claims remain generic enough to read on the teachings of the prior art. Specific dissolution profiles are not being claimed herein, other than some degree (i.e., 70%) of overlap of therapeutic activity between first and second active agents. It is the position of the Examiner that there would be overlap to some extent between the first and second active agents disclosed by the prior art. Moreover, the argument of the extent of effective plasma concentration provided by promethazine (i.e., up to 12 hours) is not being claimed. Thus, the arguments made do not represent the scope of the claims as presently recited.

The rejections of Fanara in view of Paradissis have been maintained herein.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

--No claims are allowed at this time.

This application contains claims 25, 26 and 39-67 drawn to an invention nonelected with traverse in the reply filed on 05/04/07. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday during regular business hours. (Wednesdays - Telework).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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Art Unit 1615

November 18, 2007

HUMERA N SHEIKH
PRIMARY EXAMINER